REMARKS

Claims 1 through 17 and new Claim 18 are pending in the application.

The Abstract has been amended to correct a typographical error. Support for this Amendment can be found in the Application-as-filed, for example in Claim 11 as-filed.

Claim 1 has been amended to emphasize advantageous transdermal therapeutic systems in which the active ingredient-containing polymer layer comprises at least one pressure-sensitive adhesive polymer selected from the group of carboxyl group-free polyacrylates and the transdermal therapeutic systems contain an additional active ingredient-containing layer. Support for this amendment can be found in the Application as filed, for example on Page 6, lines 12 through 15 and Page 12, lines 3 through 13 (Example 2).

Claim 1 has further been amended to emphasize that such advantageous transdermal therapeutic systems release the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ h over the period between 24 hours after administration to 72 h after administration. Support for this amendment can be found in the Application as filed, for example on Page 11, lines 17 through 20.

Claim 1 has also been amended to reflect that the active ingredient pramipexol is present within the first adhesive layer in a proportion of between 10 and 40 % by weight. Support for this amendment can be found in the Application as filed, for example on Page 10, lines 8 through 12.

Claim 2 has been amended to reflect advantageous transdermal therapeutic systems further comprising at least one element selected from the group consisting of a pressure-sensitive adhesive layer, a membrane which controls the rate of release of pramipexol, an active ingredient-containing layer or a supporting layer. Support for this amendment can be found in the Application as filed, for example on Page 6, lines 12 through 18.

Claim 3 has been amended to reflect advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive polymer is a carboxyl group-free polyacrylate prepared by polymerization of a monomer mixture of at least one acrylic ester or methacrylic ester with linear, branched or cyclic aliphatic C_1-C_{12} substituents without other functional groups, and at least one hydroxyl group-containing acrylic ester or one hydroxyl group-containing methacrylic ester in a proportion by weight of less than 10%. Support for this amendment can be found in the Application as filed, for example in Claims 4 and 5 as-filed.

Claim 4 has been canceled, as its subject matter has been incorporated into Claim 3 as-amended.

Claim 5 has been canceled, as its subject matter has been incorporated into Claim 4 as-amended.

Claim 13 has been canceled, as its subject matter has been incorporated into Claim 1 as-amended.

Claim 14 has been amended to conform to Claim 1 as-amended.

Claim 16 has been amended to depend from Claim 3 and to additionally reflect advantageous pressure-sensitive-adhesive monomer mixtures additionally comprising vinyl acetate in a proportion of less than 25% by weight. Support for this amendment can be found in the Application as filed, for example on Page 9, line 35 through Page 10, line 5.

Claim 17 has been amended to depend from Claim 1.

Claim 18 has been added to complete the record for examination and highlight advantageous embodiments of the invention.

Claim 18 is directed to advantageous transdermal therapeutic systems for continuous administration of pramipexol that advantageously include a first active ingredient-containing polymer layer comprising pramipexol in a proportion of between 10 and less than 75 % by weight and a second active ingredient-containing polymer layer comprising pramipexol in a proportion of between 2 and 10 % by weight, in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates, and the transdermal therapeutic system releases the pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters. Support for Claim 18 can be found in the Application as filed, for example on Page 12, lines 3 through 13 (Example 2) in conjunction with Page 10, lines 8 through 13 and Page 11, lines 17 through 20 and Page 8, lines 13 through 18.

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

Section 112 Rejection

Claim 1 through 17 stand rejected over the recitation "present therein." Without addressing the merits of the rejection and solely to advance prosecution of the above-referenced case, Claim 1 has been amended to reflect that the active ingredient pramipexol is present within the first adhesive layer in a proportion of between 10 and 40 % by weight. Support for this amendment can be found in the Application as filed, for example on Page 10, lines 8 through 12.

Accordingly, Applicants respectfully request withdrawal of the foregoing rejection.

The Claimed Invention is Patentable

in Light of the Art of Record

Claims 1, 3 through 6, 14 and 16 stand rejected as anticipated by WIPO Published Application WO 03/015779, whose United States Equivalent is United States Publication 2004/0247656, which has subsequently matured into United States Patent No. 7,344,733 (US 733) to Beier et al.

Claims 1 through 17 stand rejected over US 733 in view of United States Patent No. 5,112,842 (US 842) to Zierenberg et al. and WIPO publication WO 96/39136 (WO 136) to Patel et al.

It may be useful to consider the invention as recited in the claims before addressing the merits of the rejection.

Transdermal therapeutic systems (TTSs) provide a promising option for the continuous delivery of active ingredients over a prolonged period of time. TTSs deliver an active ingredient continuously and in a controlled manner to the patient's skin. After passing through the various layers of skin, the active pharmaceutical ingredient is taken up by the underlying blood vessels. The continuous delivery results in particularly uniform plasma levels. TTSs provide the additional benefit of avoiding the gastrointestinal tract, in contrast to oral forms of administration.

Unfortunately, the delivery of a sufficient quantity of active ingredients in a controlled manner over a prolonged time period via mass diffusion, initially through the TTS and subsequently the dermis, is quite challenging. Furthermore, the TTS must be sufficiently comfortable to be worn over the prolonged delivery time, e.g. the TTS must be as thin and flexible as possible.

Surprisingly, Applicants have found advantageous transdermal therapeutic systems for continuous administration of pramipexol that include both first and second pramipexol-containing polymer layers formed from pressure-sensitive adhesive polymer based on carboxyl group-free polyacrylates, in which the first pramipexol-containing polymer layer includes pramipexol in a proportion of between 10 and 40 % by weight, provides a flux rate of greater than 5 $\mu g/cm^2$ h over the period between 24 hours after administration to 72 hours after administration. In contrast, TTSs incorporating adhesives having carboxyl functional groups in the polymer, i.e. adhesives produced with acrylic acid or methacrylic acid, were found to be unsuitable for production. In that regard, the Examiner's attention is kindly directed to the Application-as-filed on Page 13, lines 20 through 24.

Altogether unexpectedly, the incorporation of two pramipexol-containing polymer layers, e.g. a "reservoir layer" layer containing a higher loading of pramipexol in addition to a "pressure adhesive layer" containing a much more moderate loading of pramipexol, both of which are formed from pressure-sensitive adhesive polymer based on carboxyl group-free polyacrylates, provides a higher flux rate at 24 hours and a more constant dosage over the course of 72 hours in comparison to a comparable TTS containing pramipexol within a single layer. In that regard, the Examiner's attention is kindly directed to the Application-as-filed, particularly to Page 12, lines 3 through 33 and Figures 1 and 2. For example, the inventive two-layered-active-ingredient TTSs provided a flux rate greater than 5 $\mu g/cm^2$ hr at the 24 hour mark. In contrast, a comparable single-layered-active-ingredient TTS provided a flux rate of less than 1 $\mu g/cm^2$ hr at 24 hours. In that regard, the Examiner's attention is kindly directed to the Application-as-filed, particularly a comparison of Figures 1 and 2 at 24 hrs.

In particularly advantageous embodiments, the inventive TTSs include a first active ingredient-containing polymer layer, i.e. a reservoir layer, comprising pramipexol in a proportion of between 10 and less than 75 % by weight and a second active ingredient-containing polymer layer comprising pramipexol in a proportion of between 2 and 10 % by weight, in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates. The TTSs likewise

advantageously release pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over a period of between 24 to 72 hours after administration, even in the absence of any excipients or penetration-promoters, as recited in newly added Claim 18.

The cited references do not teach or suggest the claimed invention.

US 733 is generally directed to directed to single layer TTSs providing improved shelf stability that include a maximum of 15 % by weight active ingredient. (Col. 2, line 66 - Col. 3, line 2 and Col. 2, lines 19 - 20). US 733 provides a generic laundry list of suitable pressure sensitive adhesives, including polyurethane. (Col. 3, lines 23 – 26). US 733 notes acrylic acid and methacrylic acid as suitable monomers within its matrix polymer. (Col. 3, lines 50 – 52). US 733 notes that permeation enhancers may be included "where applicable." (Col. 2, lines 40 – 45). The working examples of US 733 expressly teach the incorporation of permeation enhancer, i.e. Copherol®, in conjunction with acrylic-based matrix layers, however. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)). The working examples of US 733 further teach the incorporation of 2.5 to 3 weight % active ingredient within acrylic-based matrix layers. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)).

US 733 thus does not teach or suggest the claimed invention.

As indicated by the Examiner, US 733 does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration, as recited in the claims as-amended.

Nor does US 733, generally directed to single layer TTSs, teach or suggest advantageous TTSs including a first active ingredient-containing polymer layer and an additional active ingredient layer, as further recited in Claim 1 as-amended.

US 733, generically noting any of a laundry list of adhesives and a maximum of 15% active ingredient, further does not teach or suggest active ingredient-containing polymer layers formed from carboxyl group-free polyacrylates, much less such polymer layers including up to 40 40 % by weight pramipexol, as additionally recited in Claim 1 as-amended.

And US 733 most certainly does not teach or suggest advantageous transdermal therapeutic systems for continuous administration of pramipexol that include a first active ingredient-containing polymer layer comprising between 10 and less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates, and the transdermal therapeutic system releases the pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters, as recited in newly added Claim 18. In fact, US 733 teaches away from such advantageous embodiments by expressly teaching the use of permeation enhancers, i.e. Copherol®, in conjunction with its acrylic-based matrix layer.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 733, considered either alone or in combination with the remaining art of record.

The secondary references do not overcome the deficiencies in US 733.

US 842 is directed to single-active-ingredient-layer TTSs that further include a backing layer which "secure[s] the system to the skin." (Col. 2, lines 11 – 15). The working examples of US 842 include 9 wt % active substance within the single layer. (Col. 2, lines 53 – 62). US 842 curiously provides concentration data beginning on the 3rd day following application. (Col. 3, lines 2 – 12).

US 842, solely directed to single-active-ingredient-layer TTSs, does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr at 24 hours after administration, as recited in the claims as-amended. Applicants respectfully submit that single-layered-active-ingredient TTSs would instead be expected to perform poorly at the 24 hour mark, as indicated in Figure 2 of the Application-as-filed.

Nor does US 842 teach or suggest advantageous TTSs including a first active ingredient-containing polymer layer and an additional active ingredient layer, as further recited in Claim 1 as-amended.

US 842 generically noting an acrylic adhesive and a maximum of 30 % active ingredient, further does not teach or suggest active ingredient-containing polymer layers formed from carboxyl group-free polyacrylates, much less such polymer layers including up to 40 % by weight pramipexol, as additionally recited in Claim 1 as-amended.

And US 842 most certainly does not teach or suggest advantageous transdermal therapeutic systems for continuous administration of pramipexol that include a first active ingredient-containing polymer layer comprising between 10 and less than 75 % by weight of pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10% by weight pramipexol , in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates, and the transdermal therapeutic system releases the pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters, as recited in newly added Claim 18.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 842, considered either alone or in combination with the remaining art of record.

WO 136 is merely directed to the use of active ingredient in free base form in transdermal formulations. (Page 1, line 34 – Page 2, line 5). WO 136 discloses that the transdermal assembly may be provided with a two compartment reservoir having a rupturable barrier to form the free base. (Page 2, line 37 – Page 3, line 2). WO 136 generically teaches that the drug substance may be suspended in a gel. (Page 2, lines 18 – 19). WO 136 notes that its unit doses are intended for once-a-day application. (Page 3, lines 24 – 26). The working examples of WO 136 include a single drug-containing layer formed from either a saline/propylene glycol "vehicle" or a hydrogel along with a separate adhesive layer. (Page 4, lines 14 – 36). WO 136 merely provides penetration data based upon the percutaneous penetration of saturated saline or saline/propylene glycol solutions, however. (Page 5, lines 1 – 21).

WO 136, directed to TTSs for daily application, does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ h at 72 hours after administration, as recited in the claims as-amended.

Nor does WO 136, solely directed to single-layered-active-ingredient TTSs, teach or suggest advantageous TTSs including a first active ingredient-containing polymer layer and an additional active ingredient layer, as further recited in Claim 1 as-amended.

WO 136, teaching drug dispersion within a hydrogel, further does not teach or suggest active ingredient-containing polymer layers formed from carboxyl group-free polyacrylates, much less such polymer layers including up to 40 % by weight pramipexol, as additionally recited in Claim 1 as-amended.

And WO 136 most certainly does not teach or suggest advantageous transdermal therapeutic systems for continuous administration of pramipexol that include a first active ingredient-containing polymer layer comprising between 10 and less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free

polyacrylates, and the transdermal therapeutic system releases the pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters, as recited in newly added Claim 18.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of WO 136, considered either alone or in combination with the remaining art of record.

There would have been no motivation to have combined US 733, US 842 and WO 136. Applicants respectfully submit that merely because the references can be combined is not enough, there must still be a suggestion. MPEP 2143.01

However, even if Applicants had combined US 733, US 842 and WO 136 (which they did not), the claimed invention would not have resulted.

The combination more particularly does not teach or suggest transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ h at 24 to 72 hours after administration, as recited in the claims as-amended.

Nor does the combination teach or suggest advantageous TTSs including a first active ingredient-containing polymer layer and an additional active ingredient layer, as further recited in Claim 1 as-amended.

The combination further does not teach or suggest active ingredient-containing polymer layers formed from carboxyl group-free polyacrylates, much less such polymer layers including up to 40 % by weight pramipexol, as additionally recited in Claim 1 as-amended.

And the combination most certainly does not teach or suggest advantageous transdermal therapeutic systems for continuous administration of pramipexol that include a first active ingredient-containing polymer layer comprising between 10 and less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and

10 % by weight pramipexol, in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates, and the transdermal therapeutic system releases the pramipexol with a flux rate greater than 5 $\mu g/cm^2$ h over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters, as recited in newly added Claim 18. In fact, the primary reference teaches away from such advantageous embodiments.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of each of US 733, US 842 and WO 136, considered either alone or in combination with the remaining art of record.

Applicants respectfully submit that the Office Action's urging on Page 10, last paragraph, comparing the release rate of scopolamine, fentanyl and estrogen-progestin patches with rates attainable for pramipexol TTSs is pure conjecture. Applicants more particularly respectfully submit that the chemical structures of scopolamine, fentanyl and estrogen-progestin each differs significantly from the claimed pramipexol, and that the physical properties (inter alia the solubilities, mass transport properties and efficacies) of such widely differing compounds thus can not be imputed to the recited pramipexol. Applicants respectfully submit that the Office Action is instead indulging in impermissible hindsight analysis by merely picking and choosing elements from the prior art while using the instant specification as the guide for that selection process.

CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 3, 6 through 12 and 14 through 18 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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